



Antimicrobial Stewardship:

Arizona Partnerships Working to Improve the Use of Antimicrobials in the Hospital and Community

Part 8

“Antibacterials – indeed, anti-infectives as a whole – are unique in that misuse of these agents can have a negative effect on society at large. Misuse of antibacterials has led to the development of bacterial resistance, whereas misuse of a cardiovascular drug harms only the one patient, not causing a societal consequence.”

- Glenn Tillotson; Clin Infect Dis. 2010;51:752

“...we hold closely the principles that antibiotics are a gift to us from prior generations and that we have a moral obligation to ensure that this global treasure is available for our children and future generations.”

- David Gilbert, et al (and the Infectious Diseases Society of America). Clin Infect Dis. 2010;51:754-5

A Note To Our Readers and Slide Presenters

The objectives of the Subcommittee on Antimicrobial Stewardship Programs are directed at education, presentation, and identification of resources for clinicians to create toolkits of strategies that will assist clinicians with understanding, implementing, measuring, and maintaining antimicrobial stewardship programs.

The slide compendium was developed by the Subcommittee on Antimicrobial Stewardship Programs (ASP) of the Arizona Healthcare-Associated Infection (HAI) Advisory Committee in 2012-2013.

ASP is a multidisciplinary committee representing various healthcare disciplines working to define and provide guidance for establishing and maintaining an antimicrobial stewardship programs within acute care and long-term care institutions and in the community.

Their work was guided by the best available evidence at the time although the subject matter encompassed thousands of references. Accordingly, the Subcommittee selectively used examples from the published literature to provide guidance and evidenced-based criteria regarding antimicrobial stewardship. The slide compendium reflects consensus on criteria which the HAI Advisory Committee deems to represent prudent practice.

Disclaimers

All scientific and technical material included in the slide compendium applied rigorous scientific standards and peer review by the Subcommittee on Antimicrobial Stewardship Programs to ensure the accuracy and reliability of the data. The Subcommittee reviewed hundreds of published studies for the purposes of defining antimicrobial stewardship for Arizonan clinicians. The Arizona Department of Health Services (ADHS) and members of its subcommittees assume no responsibility for the opinions and interpretations of the data from published studies selected for inclusion in the slide compendium.

ADHS routinely seeks the input of highly qualified peer reviewers on the propriety, accuracy, completeness, and quality (including objectivity, utility, and integrity) of its materials. Although the specific application of peer review throughout the scientific process may vary, the overall goal is to obtain an objective evaluation of scientific information from its fellow scientists, consultants, and Committees.

Please credit ADHS for development of its slides and other tools. Please provide a link to the ADHS website when these material are used.

Introduction to Slide Section

Reasons to Optimize Antibiotic Use

Pathways to a Successful ASP

Antimicrobial Stewardship: Making the Case

ASPs: Nuts & Bolts

Antimicrobial Stewardship: Measuring Antibiotic Utilization

Antimicrobial Stewardship: Daily Activities

Antimicrobial Stewardship: Computerized & Clinical Decision Support Services

Microbiology: Cumulative Antibigram & Rapid Diagnostics

Antimicrobial Stewardship Projects: Initiation & Advanced

Antimicrobial Stewardship Barriers & Challenges: Structural & Functional

Antibiotic Use in the Community

Opportunities to Justify Continuing the ASP

Antimicrobial Stewardship: Perspectives to Consider

Summary

- **Preface:**

The microbiologist could be your new best friend early in the ASP development and implementation process. A strong relationship can assist in development of the antibiogram, implementation of rapid diagnostics, selection of antimicrobials on susceptibility panels, and susceptibility reporting policies. The clinical laboratory can assist in capturing data, such as turnaround time for diagnostics and notification processes to prescribers and pharmacy.

- **Content:**

15 slides with 1 additional slide.

- **Suggestions for Presentation:**

Appropriate audience would be microbiologists, including their directors, and the ASP committee. The presentation could be given in 30 minutes with time for questions and discussion. Alternatively, this is part of the self-learning modules for antimicrobial stewardship.

- **Comments:**

Also, refer to the antibiogram toolkit made available on the ADHS website. Clinical examples from the literature are provided for discussion. Newer technologies are reviewed including procalcitonin.

MICROBIOLOGY LABORATORY, THE CUMULATIVE ANTIBIOGRAM, AND RAPID DIAGNOSTICS

**[ALSO, REFER TO THE ANTIBIOGRAM TOOLKIT PROVIDED BY THE
HEALTHCARE-ASSOCIATED INFECTIONS PROGRAM ON THIS WEBSITE]**

The Clinical Microbiologist: ASPs New Best Friend

- Microbiologists are an essential team member of the antibiotic stewardship team
- Incorporate antibiogram data into point of decision antibiotic prescribing
- Create real-time alerts of key pathogens
 - Resistant Gram-negative bacteria [(e.g., extended spectrum B-lactamase (ESBL)+, carbapenem resistant Enterobacteriaceae (CRE)], daptomycin-nonsusceptible MRSA, INH-resistant or MDR-TB, fluconazole-resistant *Candida albicans*
- Collaborate in the selection of testing panels aligned with the antibiotic formulary
- Add notes to culture reports when appropriate
 - Explanation of susceptibility reports for ESBLs and KPCs
 - Suggestions of when to consult the ID service
- Education of prescribers when specimens are not appropriate for culture
 - Saliva (vs sputum), urine specimens with low bacterial counts on microscopy, skin swabs (vs deep tissue, curettage, sterile sites)
- Facilitate saving isolates for additional testing and research
 - Unusual resistance patterns or rare pathogens
 - Molecular analyses

Example of Selective Reporting on Culture and Sensitivity Result

Footnotes:

- Report “only use if severe allergy to penicillin is documented”
- Institution’s drug dosing guidelines may suggest lower dose, e.g., cefepime 1gm IV Q12H, or ciprofloxacin 250mg PO/200 IV Q12H to 500mg PO/400mg IV Q12H, x 5 days
- For more serious infections, pathology note may suggest cefepime 1gm IV Q6H or 2gm IV Q8H, or ciprofloxacin 400mg Iv Q8H if normal renal function
- Note may suggest combination with an anti-pseudomonal beta-lactam
- Serum peak/MIC ratio is generally optimal for tobramycin, e.g., C_{max}/MIC > 8 even if isolate is S to gent and tobra

GNB Susceptibility Card Results	Susceptibility Interpretation	What You Report (if urine culture)	What You Report (if blood culture)
Amikacin	S		
Aztreonam	S		X ^a
Cefepime	S	X ^b	X ^c
Ceftazidime	S		
Ciprofloxacin	S	X ^b	X ^c
Gentamicin	S	X	
Imipenem	S		
Levofloxacin	S		
Meropenem	S		
Pip/tazobactam	S		
Tobramycin	S		X ^{d,e}

Example above assumes the institution does not stock ceftazidime or levofloxacin although these agents may be part of the testing card; monomicrobial infection; nitrofurantoin not represented in this example

Effect of Antimicrobial Stewardship on Resistance is Difficult to Evaluate

- Changes in resistance observed from sequential antibiogram data cannot be easily linked to effects of antimicrobial stewardship on prescribing
- Antibiograms are generally inadequately designed to reflect changes in resistance patterns as a result of changes in hospital antibiotic use
 - Antibiograms include data on bacterial isolates from patients with infections, but also include those that represent colonization
 - Antibiogram reporting policies (i.e., duplicate reporting) may change making analyses over time difficult
 - Bacterial isolates in hospitalized patients may represent community-onset infections (cultures obtained in ED or <48 hours following admission) or may reflect antibiotic exposures at other facilities or as an outpatient (“importation” of resistance)
 - Hospital-wide antibiograms may be less useful for areas with higher prevalence of drug resistance (e.g., ICU)
 - Antibiograms do not accurately assess specific interventions at a specific time period
 - Antibiograms cannot detect emergence of MDRO phenotypes
- Antibiograms include “first isolate” whose susceptibility may not reflect previous antibiotic exposure; tracking “last isolate” may better reflect the impact of antibiotics

Effect of Antimicrobial Stewardship on Resistance is Difficult to Evaluate (cont'd)

- Resistance has two dimensions: population-based and patient-specific (ASP interventions may affect the latter without showing a change in the former)
 - Antibigrams pool the same isolates obtained from the entire hospital population
 - Antibigrams may fail to study patient-specific groups, such as pediatric cystic fibrosis, neuro ICU vs surgical ICU, *Pseudomonas aeruginosa* from respiratory isolates versus urinary tract isolates, etc.
 - Beneficial effects of an ASP in facilitating appropriate antimicrobial use may be diluted by the larger population inclusive in an antibiogram
- The existing literature has several limitations
 - Most studies are quasi-experimental and study short pre-/post-intervention periods
 - Studies on hospital-onset *C. difficile* rates may not account for the influence of other factors, such as improved environmental cleaning or change in isolation policies
 - Interrupted time-series analysis can help demonstrate the effectiveness of an ASP in reducing resistance, but this tool is complex and requires a large amount of data; yet it has the best chance to provide findings which support a favorable impact of ASP interventions on bacterial resistance

Antimicrobial resistance is multifactorial; antimicrobial exposure is only one of many possible reasons for the emergence or spread of drug-resistant organisms

Does Antibiotic Switching Result in Decreased Resistance?

- Two-year study to examine the effect of restricting cephalosporins to control an ESBL-producing *Klebsiella* outbreak¹
- Cephalosporins were allowed only for surgical prophylaxis, bacterial meningitis, spontaneous bacterial peritonitis, and gonococcal disease¹
- Results¹:

The Good News	The Bad News
80% reduction in cephalosporin use	141% increase in imipenem use
44% reduction in ceftazidime-resistant <i>Klebsiella pneumoniae</i>	69% increase in imipenem-resistant <i>Pseudomonas aeruginosa</i>

- “Squeezing the balloon” should be avoided; essentially trading one antibiotic resistance problem for another²
- There is insufficient data to recommend antibiotic switching or cycling to decrease drug resistance per IDSA/SHEA guidelines²

Modeling of resistance transmission suggests diversity of antibiotics have the greatest potential to decrease resistance

1 Rahal J et al. JAMA. 1998;280:1233-7.

2 Dellit TH, et al. Clin Infect Dis. 2007;44:159-77.

Example: The Effect of an Antimicrobial Formulary Change on Hospital Resistance Patterns

- Reduce the use of ceftazidime and cefotaxime and replace with cefepime
- Two 6-month periods before and after the formulary change
- 5 selected MDRO phenotypes were studied
- Results between two 6-month periods:
 - Ceftazidime use decreased from 9600 grams to 99 grams; cefotaxime use decreased from 6314 grams to 732 grams (combined decrease 89%)
 - Cefepime increased from 0 gram to 5396 grams (64% decrease over combined use of other 2 cephalosporins)
 - Infections due to ceftazidime-R *K.pneumoniae* decreased from 13% to 3%, piperacillin-R *P.aeruginosa* decreased from 22% to 14%, and ceftazidime-R *P.aeruginosa* decreased from 25% to 15% ($p < 0.05$ for all)
 - Infections from MRSA dropped insignificantly and VRE infections increased significantly

Rapid Diagnostic Testing and Antimicrobial Stewardship: The Advantage of Early Knowledge

- Time required for bacterial identification and susceptibility testing have critical impact on guiding therapy, and coupled with timely communication, can result in increased appropriateness of therapy ¹
- Several commercial assays are available for the rapid identification of *Staphylococcus* species, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Clostridium difficile*, and *Candida* species ¹
- Detection times are measured in hours, typically 1-2 hours
 - Using traditional techniques, the average time required for a microbiology laboratory to deliver antimicrobial susceptibility testing results to a clinician is 40 hours ²
- Commercial methods include PNA-FISH, PCR, MALDI-TOF, and rapid antigen detection

1 Goff D, Jankowski D, Tenover F. Pharmacotherapy. 2012;32(8):677-87

2 Kerremans J et al. J Antimicrob Chemother. 2008;61:428-35.

Rapid Diagnostic Testing Integrated into ASPs May Deliver Favorable Outcomes

- Rapid differentiation of *S.aureus* and coagulase-negative staphylococci in positive blood cultures
 - PNA-FISH vs traditional methods: reduction in median length of stay from 6 to 4 days ($p<0.05$), a trend toward less vancomycin use from 6.78 DDD to 4.9 DDD in patients not in the ICU, and a decrease in hospital costs of \$4005/patient ¹
 - Rapid PCR vs historical control: a 1.7-day decrease in time to optimal antimicrobial therapy for MSSA bacteremia ($p=0.002$), a decrease in length of stay of 6.2 days ($p=0.07$), and a decrease in mean hospital cost by \$21,387/episode of *S. aureus* bacteremia ($p=0.02$) when an infectious disease ²
- PNA-FISH, *C.albicans* versus non-albicans *Candida* in fungemia
 - Savings of \$1,837/patient treated, mostly with decreased caspofungin use ³

1 Forrest G et al. J Antimicrob Chemother. 2006;58:154–8.

2 Bauer K et al. Clin Infect Dis. 2010;51:1074–80.

3 Alexander B et al. Diag Microbiol Infect Dis. 2006;54:277-82.

Example: An ASP's Impact with Polymerase Chain Reaction MRSA/*S.aureus* Blood Culture Test

- Evaluated clinical and economic outcomes of a rapid polymerase chain reaction (rPCR) methicillin-resistant *S.aureus*/*S.aureus* blood culture test
- Single-center (pre-rPCR vs post-rPCR) study compared inpatients with *S.aureus* bacteremia
- An ID pharmacist was contacted with results of the rPCR; effective antibiotics and an infectious diseases consult were recommended
- Clinical and economic outcomes in 156 patients:
 - Mean time to switch from empiric vancomycin to cefazolin or nafcillin in patients with MSSA bacteremia was 1.7 days shorter post-rPCR ($P=0.002$); and mean time to switch from vancomycin to daptomycin in patients with MRSA bacteremia was 5.5 days shorter post-rPCR ($P=0.15$)
 - Mean time to ID consult decreased (9 days pre-rPCR to 3 days post-rPCR; $P=0.25$)
 - In the post-rPCR MSSA and MRSA groups, the mean LOS was 6.2 days shorter (21.5 to 15.3 days; $P=0.07$)
 - The total mean hospital costs were \$21,387 less (\$69,737 to \$48,350; $P=0.02$)
 - Mean ICU costs decreased by \$9,930 ($P=0.03$)
 - Mean pharmacy costs were decreased by \$2,918 ($p=0.08$)

Example: Polymerase Chain Reaction (PCR) Used in an ASP Intervention for Coagulase-Negative Staphylococci

- Evaluate the impact of interventions by an ASP team on the duration of anti-staphylococcal antibiotic therapy, hospital LOS, and related costs
- Quasi-experimental pre- and post-intervention study (53 inpatients; 31 pre-intervention and 22 post-intervention) in patients with positive blood cultures for coagulase-negative staphylococci (CoNS) identified by PCR
- Intervention made when blood culture result was determined to be a contaminant
- Excluded patients < 18yo or >89yo, neutropenia, incomplete records, and duplicate or mixed blood cultures
- Results (pre- vs post-intervention periods):
 - Antistaphylococcal antibiotics discontinued 32 hrs sooner from time of PCR (median 57.7 vs 25.7 hrs; $p=0.005$)
 - Total antibiotic exposure decreased 43.5 hrs (97.6 vs 54.1 hrs; $p=0.011$)
 - Infection-related LOS decreased 4.5 days (10 vs 5.5 days; $p=0.018$)
 - Infection-related costs decreased \$8338 (\$28,973 vs \$20,635; $p=0.144$)
 - The pharmacist initiated vancomycin in 7 (21.9%) patients with CoNS bloodstream infections

Even Newer Technologies Being Analyzed For Opportunities in ASPs

- Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS) uses a new technology to identify bacteria and yeast from agar plate colonies
 - The time from putting the target plate into the instrument to final result is fast, within a few minutes ¹
- Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS) coupled with ASP and rapid antimicrobial susceptibility testing ²
 - The mean hospital length of stay in the preintervention group survivors (n=100) was 11.9 versus 9.3 days in the intervention group (n=101; P=0.01)
 - Mean hospital costs per patient were \$45,709 in the preintervention group and \$26,162 in the intervention group (P=0 .009)

1 Patel R. Clin Infect Dis. 2013;57(4):564-72.

2 Perez K et al. Arch Pathol Lab Med. 2012; doi:10.5858/arpa.2012-0651-OA

Is It Time for Procalcitonin (PCT) – A Biomarker of Systemic Inflammation Used in Diagnosing Bacterial Infections?

- Schuetz et al concluded in a review that inclusion of PCT data in clinical algorithms improves individualized decision-making regarding use of antibiotics in patients in critical care for respiratory tract infections and sepsis¹
- A recent report from AHRQ stated that procalcitonin guidance reduces antibiotic use when used to discontinue antibiotics in adult ICU patients and to initiate or discontinue antibiotics in patients with respiratory tract infections²
 - Future research should compare procalcitonin guidance with antibiotic stewardship programs and to implementation of guidelines
 - Outcomes of high interest for future research are the consequences of reduction in antibiotic use for antibiotic resistance and for adverse events of antibiotic therapy.
- A meta-analysis by Li et al concluded that PCT-guided antibiotic therapy in patients with respiratory tract infections appears to reduce antibiotic use without affecting overall mortality or length of stay in the hospital³

1 Schuetz P, Raad I, Amin D. Curr Opin Crit Care. 2013; June 28 (epub ahead of print; <http://www.ncbi.nlm.nih.gov/pubmed/23817026>

2 Soni NJ, et al. Procalcitonin-Guided Antibiotic Therapy. Comparative Effectiveness Review No. 78. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 12(13)-EHC124-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

3 Li H et al. Antimicrob Agents Chemother. 2011;55(12):5900-6.

Summary: Value Your Microbiologists

- The clinical microbiology laboratory plays a critical role in the timely identification of microbial pathogens, performance of susceptibility testing, identification and molecular epidemiologic investigation of local outbreaks of infection, and resistance surveillance
 - These roles are in flux: changing breakpoints in Gram-negative bacteria, advances in molecular diagnostics and rapid testing, improved computer surveillance, and use of biomarkers to potentially avoid the need for extended courses of broad-spectrum empirical therapy
- The ASP includes the clinical microbiologist as an integral member of the AST to assist in the prudent use of antimicrobials and direct appropriate therapy based on local guidelines
 - Development and publication of the antibiogram
 - Prioritization of tested antimicrobials
 - Selective reporting of susceptibility profiles (e.g., not routinely reporting susceptibility of *S. aureus* to rifampin to prevent inadvertent monotherapy with rifampin)
 - Clonal characterization of resistant and outbreak strains (resistant strains which are diverse may be approached with antimicrobial interventions)

ADDITIONAL SLIDES

Comparative Susceptibility Reporting Tracks Resistance in the U.S. and Globally

- Large national or global susceptibility testing programs provide insight into methodologies, resistance patterns by site of infection, and MIC distributions (in relation to breakpoints)
- May provide comparative data, MIC distributions (generally, not in Vitek/MicroScan), novel resistance mechanisms
- Sponsors are generally committed to report annual surveillance data for 5 years following FDA approval; many continue past this according to commercial interests

Surveillance Study	Characteristics
ABC Active Bacterial Core Surveillance (CDC)	Annual susceptibility data for Group A /B streptococci, MRSA, <i>N.meningitidis</i> , <i>S.pneumoniae</i> , <i>H.influenzae</i>
AWARE Assessing Worldwide Antimicrobial Resistance Evaluation (Forest)	Ceftaroline global susceptibilities for Gram-positive and Gram-negative pathogens encountered in pneumonia
EARSS European Antimicrobial Resistance Surveillance System	Participation by dozens of countries in Europe; hospital and community
MYSTIC and OPTAMA (PK-PD) Meropenem Yearly Susceptibility Test Information Collection (Astra-Zeneca)	Many publications Global reports
SENTRY Support from several sources, including government and pharma	Global reports since 1997 Longest ongoing surveillance Ron Jones, PhD; JMI Labs
TEST Tigecycline Evaluation and Surveillance Trial (Pfizer)	Studies in staphylococci, Gram-negatives, and anaerobes
TRUST Tracking Resistance in the US Today (Ortho-McNeil)	Originally <i>S.pneumoniae</i> susceptibilities; included gram-negatives later; not many publications
ZAAPS and LEADER (USA) Zyvox Annual Appraisal of Potency and Spectrum (Pfizer)	Linezolid susceptibilities against large collections of Gram-positive pathogens